Characteristics of Deliveries Resulting in Neonatal Hypoxic Ischemic Encephalopathy: A Multi-Centred Retrospective Case Series

Mark Hehir[1], Richard Berkowitz[1], Christian Pettker[2], Neil Seligman[3], Mary DAlton[4], Maria Andrikopoulou[5], Stephanie Havens[3], Yongmei Huang[5], Joses Jain[5], Krista Mehlhaff[2], and Alex Friedman (USA)[5]

[1]Columbia University, College of Physicians and Surgeons
[2]Yale University School of Medicine
[3]University of Rochester Medical Center
[4]Columbia University
[5]Columbia University College of Physicians and Surgeons

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Abstract

OBJECTIVE: To characterize clinical management of deliveries resulting in neonatal hypoxic ischemic encephalopathy. DESIGN: Retrospective case series SETTING: Three academic referral medical centers in the United States POPULATION: All neonates [?]35 weeks' gestation with HIE based on cord blood pH<7.0, base deficit of [?]12.0mmol/L, along with relevant radiological, laboratory, and clinical findings. METHODS: Clinical management was characterized based on whether (i)delivery occurred within 120 minutes of presentation, (ii)delivery occurred due to a sentinel event such as cord prolapse or uterine rupture, and (iii)the fetal heart rate tracing(FHR) demonstrated variability, accelerations, or both upon presentation and in the half hour before delivery. MAIN OUTCOME MEASURES: Relationship of mode of delivery to FHR tracing characteristics at delivery. Obstetric outcomes, labour course and management were analysed. RESULTS: Of 144,904 deliveries, 102 maternal-newborn dyads met criteria. Of these, 19 delivered within 120 of minutes of presentation and four further women experienced a sentinel event. Of the remaining 79, 66(84%) had a FHR tracing on presentation that demonstrated variability, accelerations or both. Of these 66 cases, 27 had a fetal heart tracing that demonstrated variability, accelerations or both in the 30 minutes preceding delivery. CONCLUSION: Approximately two-thirds of cases of HIE occurred in cases where the FHR tracing initially demonstrated variability, accelerations, or both, without a sentinel event and without a condition requiring delivery within 120 minutes of presentation. Of these >40% had variability, accelerations, or both in the half hour before delivery. This suggests additional insights are required to prevent some cases of HIE.

Introduction

Neonatal encephalopathy is defined by the American College of Obstetricians and Gynecologists and American Academy of Pediatrics joint Task Force on Neonatal Encephalopathy as a clinical syndrome of disturbed neurologic function in the earliest days of life in an infant born [?]35 weeks of gestation, manifested by a subnormal level of consciousness or seizures, and often accompanied by difficulty with maintaining respiration and depression of tone and reflexes.[1] Hypoxic-ischemic encephalopathy (HIE) accounts for a significant proportion of encephalopathic newborns, and despite advances in perinatal care, moderate-to-severe HIE remains a major cause of acute neurological injury and subsequent long-term neurodevelopmental disability.[2] While prenatal and/or postnatal complications may cause HIE, studies have demonstrated that the majority of encephalopathic newborn infants sustained brain injury at or near the time of birth.[3]

The importance of recognition of intrapartum fetal compromise followed by appropriate action is essential to mitigate the presence of effects of hypoxia and avoid subsequent disability. Obstetric leaders have called for improvements in safety and quality assessment[4] including initiatives to improve both the recognition of pathological fetal heart rate tracings[5,6] and the clinical management of sentinel events which can lead to fetal compromise.[7,8] Despite ongoing efforts to minimize the risk of neurological injury at delivery, contemporary data on patient characteristics and clinical events and management of labor preceding HIE is limited. Given that there is a significant knowledge gap regarding clinical events and management during such deliveries, the aim of this study was to undertake a structured review of a large series of deliveries of neonates with HIE.

Methods

This retrospective case series evaluated all neonates [?]35 weeks of gestation born with HIE over a ten-year study period from January 1st 2007 to December 31st 2016 at three tertiary referral academic medical centers. Institutional Review Board Approval was obtained at all three participating institutions (Columbia University Medical Centre, Yale New Haven Hospital and University of Rochester) prior to the commencement of any data collection. This study received funding in the form of an Award for the Advancement of Clinical Initiatives from MCIC Vermont, Broad St., New York, NY. MCIC Vermont did not have a role in conducting this study.

A diagnosis of HIE was based on the presence of fetal acidemia (defined as arterial cord gas pH <7.0, a base deficit of [?]12 mmol/L, or both) along with clinical findings such as an Apgar score of <5 at 5 or 10 minutes, evidence of acute brain injury on neonatal neuroimaging, or abnormal neurologic findings on neonatal clinical examination. A structured review of each case was carried out using a modified version of the template recommended by the American Academy of Pediatrics for the review of cases of neonatal encephalopathy.[9] Maternal demographic information was ascertained and risk factors such as pre-gestational and gestational diabetes, chronic hypertension, preeclampsia, and use of tobacco and recreational drugs were identified. Obstetric information obtained included gestational age at delivery, the presence of obstetric complications such as spontaneous preterm labor, preterm premature rupture of membranes, term premature rupture of membranes, placenta previa, vasa previa, trial of labor after cesarean, chorioamnionitis, antenatal bleeding, and other complications. Information about the fetus was obtained including diagnoses of fetal growth restriction based on the presence of ultrasound estimated fetal weight <10th percentile within 4 weeks of delivery, suspected macrosomia based on the presence of ultrasound estimated fetal weight >90th percentile within 4 weeks of delivery, major congenital anomalies, and prenatally diagnosed genetic abnormalities.

The labor course and management were abstracted and included total time in labor, duration of the second stage, time of rupture of membranes and whether they were ruptured artificially or spontaneously, whether amniotic fluid was clear, meconium-stained, or blood-stained, use of oxytocin for induction and augmentation, labor anesthesia, fetal presentation, time of day of delivery, and mode of delivery including whether operative delivery was performed. The presence of sentinel events including uterine rupture, umbilical cord prolapse, amniotic fluid embolus, or maternal cardiac arrest was ascertained.

Fetal heart rate (FHR) tracings were reviewed and the characteristics in the first 30 minutes of monitoring and the final 30 minutes prior to delivery were recorded. FHR characteristics evaluated included fetal heart rate baseline, the presence of accelerations, the presence of late decelerations, and whether late decelerations, if present, were recurrent (present with [?]50% of contractions). FHR tracings were categorized as category I, II or III according to the Eunice Kennedy Shriver National Institute of Child Health and Human Development consensus panel and this was also the source for our definitions for FHR characteristics.[10] Presence or absence of uterine tachysystole, as defined by the above consensus panel, was additionally evaluated. Labor course and management and fetal heart tracing findings were analyzed based upon whether patients were delivered [?]120 minutes or >120 after presentation.

Neonatal data was obtained including (i) Apgar scores at 5 and 10 minutes, (ii) venous and arterial cord blood sample pH, base deficit, pO2, and pC02, (iii) neonatal blood sample pH, base deficit, pO2, pC02, and lactate,

(iv) neonatal resuscitation including whether bag/mask, cardiopulmonary resuscitation, and intubation were required, (v) neonatal imaging including ultrasound, CT, and MRI findings, (vi) EEG results, (vii) witnessed seizure-like activity, (viii) use of head or body cooling, and (ix) presence of multi-system organ involvement. When available, placental pathology was reviewed.

Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools.[11,12]REDCap is a secure, web-based software platform designed to support data capture for research studies, providing an intuitive interface for validated data capture, audit trails for tracking data manipulation and export procedures, and automated export procedures for seamless data downloads to common statistical packages. SAS version 9.4 was used for statistical analyses (SAS Institute, Cary, NC.)

Results

In the 3 hospitals in the study, 144,904 deliveries occurred from January 1, 2007 to December 31, 2016. During this period, 102 maternal-neonate dyads met criteria and were included in the analysis. (**Table 1)** describes the maternal demographics and medical conditions. The mean gestational age at delivery was 38.4 weeks. There were 2 multiple gestations and approximately 10% of patients (10/102) attempted trial of labor after cesarean. Evaluating pregnancy complications, 22% of women had term or preterm premature rupture of membranes, 8% chorioamnionitis, 10% antenatal bleeding within 24 hours of delivery, and there was one vasa previa (**Table 2**). Prenatal diagnosis and ultrasound demonstrated growth restriction in 5% of pregnancies, suspected macrosomia in 3%, a major congenital anomaly in 6%, and a genetic abnormality in 5%.

Neonatal Findings

Evaluating neonatal findings at birth, 38% of neonates had a 5-minute Apgar score <5 (n=39), 21% had a 10-minute Apgar score <5 (n=21), 36% had an arterial cord pH <7 (n=37), and 40% (n=41) had an arterial cord base deficit of [?]12 (**Table 2**). Common neonatal findings included seizures on EEG (29%, n=30), witnessed seizures (54%, n=55), need for intubation (58%, n=59), and abnormal MRI findings (54%, n=55). Less common findings included abnormal CT findings (13%, n=13) and abnormal cranial ultrasound findings (17%, n=17). A minority of neonates required cardiopulmonary resuscitation (22%, n=22).

Women delivered [?]120 minutes after presentation

Most women were delivered >120 minutes after presentation (n=83, 81.4%) (**Figure 1**). Of the 19 women delivered [?]120 minutes after presentation, 74% (n=14) were by cesarean and 26% (n=5) were by non-operative vaginal delivery (**Table 3**). Evaluating the FHR tracings on presentation of these 19 women, 5 had decelerations, 6 had an abnormal baselines (<110 or >160 beats per minute), and 7 had a category II tracings (**Table 4**).

Women delivered >120 minutes after presentation

Of the 83 women delivered >120 minutes after presentation, 4 experienced a sentinel event (1 cord prolapse and 3 uterine ruptures). Excluding the 4 women with a sentinel event, the majority of women (84%, n=66/79) had moderate variability, accelerations, or both on presentation (in the first 30 minutes of the tracing) including moderate variability, accelerations, or both. Of the 66 women with moderate variability and/or accelerations on presentation, 40% (27/66) retained these features (moderate variability, accelerations, or both) in the final 30 minutes before delivery (**Figure 2, Table 4**). The majority of the 27 women with moderate variability and/or accelerations, prior to delivery underwent cesarean delivery (n=16). Of the 39 women without moderate variability or accelerations prior to delivery the majority were by operative (10%, n=4) or non-operative vaginal delivery (54%, n=21). Mode of delivery did not differ significantly based on the whether the FHR tracing demonstrated moderate variability and/or accelerations prior to delivery (p=0.17).

The labor courses and clinical management of the 27 women with moderate variability, accelerations, or both on presentation and prior to delivery were heterogenous (**Figure 3**). Among this group there were

2 cases of intrauterine growth restriction and 2 cases of clinical chorioamnionitis. Seven women underwent a pre-labor cesarean delivery and 1 woman underwent a cesarean delivery in the first stage of labor. The remaining 8 women underwent cesarean delivery during second stages that ranged from 62 to 428 minutes; 3 of these cesareans occurred after failed operative vaginal delivery attempts. Of the 11 women undergoing vaginal delivery 6 had a second stage [?]1 hour, 3 had a second stage 1 to [?]3 hours, and 2 had a second stage >3 hours both of which required operative vaginal delivery. Overall, 8 of the 27 women had a second stage of [?]3 hours and 7 had labor courses [?]18 hours.

Discussion

This study from three referral hospitals found that the majority of HIE cases over a 10-year period were delivered >120 minutes after presentation and did not result from sentinel events. Most cases had moderate variability, accelerations, or both on presentation, and of the cases with these FHR characteristics on presentation not delivered within 120 minutes or for a sentinel event, 40% also had moderate variability and/or accelerations, prior to delivery. Among the group of women with moderate variability, accelerations, or both prior to delivery 30% had a prolonged second stage, and significant proportions delivered either via pre-labor cesarean (26%) or vaginally with a second stage <1 hour (22%). Paradoxically, women who delivered >120 minutes after presentation with moderate variability and/or accelerations, on presentation were more likely to deliver by cesarean with moderate variability and/or accelerations, prior to delivery, although this difference was not statistically significant.

The findings from this study support the diverse clinical scenarios and labor characteristics associated with HIE and there was no common theme identified that could predict any significant proportion of HIE cases. Studies from the UK[13], South Africa[14] and New Zealand[15] have estimated the degree to which intrapartum asphyxia was associated with human factors and found preventability in 64%, 63% and 55% of cases respectively. In 38% of the cases in this study, delivery occurred in the absence of moderate variability or accelerations after these features were noted on presentation supporting the possibility of acute events occurring during labor. Of the 26% of cases that occurred with moderate variability and/or accelerations, proximal to delivery more than a quarter had a labor duration of [?]18 hours supporting the possibility that other approaches, such as the use of category II algorithms, may be required to ascertain risk beyond the presence or absence of variability or accelerations alone.[5]Overall these findings support the notion that risk reduction for HIE will likely require care improvement and management across a range of clinical scenarios, and that some outcomes may be unpreventable. Clinical chorioamnionitis and fetal growth restriction diagnoses were not particularly common among pregnancies resulting in HIE in the setting of FHR findings demonstrating moderate variability, accelerations, or both, and thus were unlikely to be important explanatory risk factors in this case series.

This study evaluated a large number of cases of HIE in three different academic medical centers. Factors leading to HIE may be challenging to study due to its infrequent clinical occurrence. The relatively large number of cases evaluated in this study allowed us to create reasonably sized groups describing labor and delivery management and risk factors, as well as fetal heart tracing characteristics that allow meaningful clinical interpretations. That we were able to include detailed data on each case facilitated comparisons across a number of clinical management parameters.

Limitations include that while the review of each case of HIE involved the thorough examination of the healthcare record by an individual researcher it is certainly possible that due to the retrospective nature of data collection some relevant material may have been omitted or inaccurately recorded. A prospective design with contemporaneous recording and a validated data collection tool may have improved the accuracy of the reported data.

Conclusion

In this large series of neonates with HIE whose intrapartum care was managed in three academic medical centers approximately two thirds of the cases occurred in the initial setting of moderate variability and/or accelerations on FHR tracing without a sentinel event. A significant proportion of cases also had moderate

variability, accelerations, or both in the half hour prior to delivery. The study findings support the concept that diverse clinical scenarios and labor characteristics may be associated with the birth of an infant with HIE, and that moderate variability and/or accelerations may not preclude the development of that disorder. These findings support the notion that risk reduction for HIE will likely involve improvement of management across a range of clinical scenarios, and that some of these outcomes may prove to be unpreventable.

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Disclosure of Interests

Dr. D'Alton has had a leadership role in ACOG II's Safe Motherhood Initiative which has received unrestricted funding from Merck for Mothers.

The remaining authors report no conflict of interest.

Contribution of Authorship

MH designed the study, gathered data and authored the manuscript. RB designed the study and authored the manuscript. CP designed the study and authored the manuscript. NS designed the study and authored the manuscript. MD designed the study and authored the manuscript. MA gathered data and authored the manuscript. SH gathered data. YH analysed data and performed statistical analysis. JJ gathered data. KM gathered data and authored the manuscript. BW gathered data. AF designed the study, gathered data and authored the manuscript.

Ethical Approval

Institutional Review Board Approval was obtained at all three participating institutions (Columbia University Medical Centre, Yale New Haven Hospital and University of Rochester) prior to the commencement of any data collection.

Figure Legends

Figure 1: Demonstrates clinical management characteristics of deliveries in the case series.

Figure 2: Demonstrates mode of delivery based on characteristics of the fetal heart tracing in the 30 minutes preceding delivery.

Figure 3: Demonstrates the labor course of deliveries complicated by HIE where the fetal heart tracing demonstrated moderate variability, accelerations, or both, both on admission and within 30 minutes of delivery (n=27). *CC*= clinical chorioamnionitis.*IUGR*= intrauterine growth restriction.

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Figure 1. Clinical management characteristics

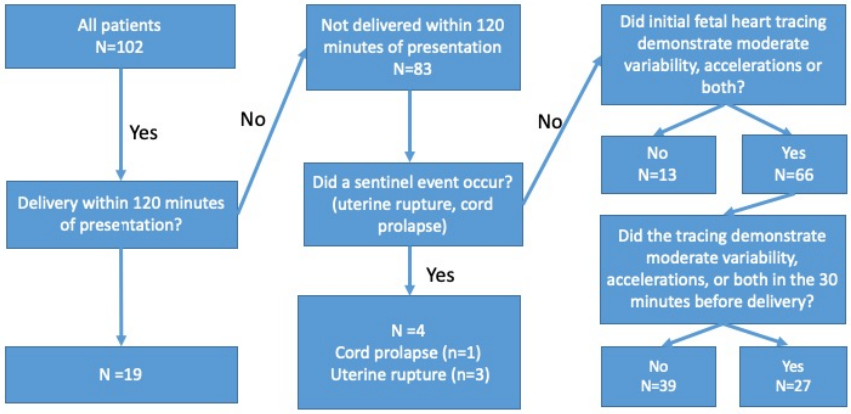

Figure 2. Mode of delivery by fetal heart rate tracing findings prior to delivery

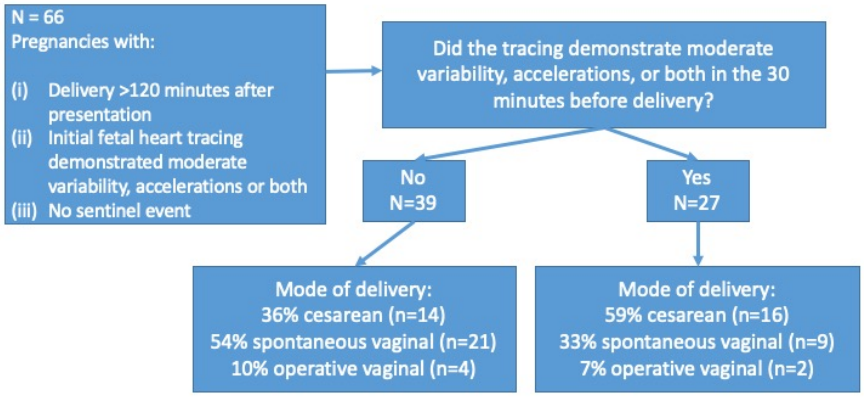

Figure 3. Labor events for patients with moderate variability, accelerations, or both prior to delivery